

**REMARKS/ARGUMENTS**

Claim 57 is pending and under examination.

Applicants thank the Examiner for the interview on March 11, 2008 in which the obviousness rejection and prior art, in particular Shen *et al.*, *Int. J. Cancer* 42:792-797, 1988 ("Shen") and Ghetie *et al.*, *Cancer Res.* 51:5876-5880, 1991 ("Ghetie") were discussed.

*Rejection under 35 U.S.C. § 103*

Claim 57 remains rejected as allegedly obvious over a combination of ten references, two of which are Shen *et al.*, *Int. J. Cancer* 42:792-797, 1988 ("Shen") and Ghetie *et al.*, *Cancer Res.* 51:5876-5880, 1991 ("Ghetie"). Evidence of secondary considerations such as unexpected results can be used to overcome a *prima facie* case of obviousness and establish the non-obviousness of a claimed invention. See, *In re Soni*, 34 USPQ2d 1684 (Fed. Cir. 1995). The Examiner alleges that the claims are obvious over the art cited in the previous office action. However, even if one of skill in the art would have arrived at the combination of the elements of the present invention (which Applicants do not concede) based on the teachings in the art, the unexpected effectiveness of the claimed compositions for treating hairy cell leukemia obviates the rejection.

In addressing Applicants' previous assertions of surprising results (see, *e.g.*, Applicants' responses filed November 7, 2007 and May 7, 2007), the Examiner contends that the evidence of record showing that the inventors consider the level of efficacy that was achieved in a phase I clinical trial to be unexpectedly high is not adequate to overcome the obviousness rejection. In particular, the Examiner alleges that the cited references strongly suggest that RFB4dsFV conjugated to PE38 would be an excellent candidate for the treatment of hairy-cell leukemia. The Examiner points to Shen as supposedly teaching "that the unusually potent cytotoxic activity of the disulfide stabilized RFB4 antibody would be excellent candidates [sic] for the systemic therapy of CD22<sup>+</sup> B-cell neoplasm" (last sentence of page 5 bridging to page 6 of the Office Action). Applicants respectfully disagree with this characterization of the disclosure in Shen and the other references cited by the Examiner.

*The cited art does not lead to an expectation of clinical efficacy at the level achieved with the claimed immunoconjugates.*

First, the passage of Shen on page 795-796 of the Discussion that was cited by the Examiner does not relate to disulfide-stabilized RFB4 antibody. Those passages relate to the immunotoxin conjugates IgG-RFB4-A and Fab'-RFB4-A. These two immunotoxins are prepared with the A chain of ricin (see, *e.g.*, the first line of the abstract, and paragraphs 1 and 2 on page 792), not PE toxin, linked to RFB4-Fab' or RFB4 IgG, not to RFB4dsFv. It is these particular ricin A chain immunoconjugates that are described by Shen as having potent cytotoxicity (see, for example page 796, referring to IgG-rFB4-A or Fab'-RFB4-A). Shen only indicates that these particular immunoconjugates are candidates for clinical trials. There is no teaching or suggestions that treatment of patients with such immunotoxins would lead to complete remissions.

Moreover, Shen only evaluates cytotoxic activity of the immunoconjugates on cells *in vitro*. Although Ghetie (also cited by the Examiner in the obviousness rejection, as noted above) shows that the RFB4 IgG and RFB4Fab' immunotoxins made with deglycosylated ricin A-chain (dgA) are cytotoxic *in vivo* in a mouse mode, these again are different immunotoxins in comparison to the immunoconjugates of the current invention. Further, Ghetie teaches that the experiments they performed compared the antitumor effect of the two immunotoxins under conditions in which the tumor cell burden is minimal (page 5879, column 1, the last sentence bridging to column 2). They did, however, perform one study in which the most potent immunotoxin (the intact RFB4 IgG-ricin A toxin) was administered at a late stage of tumor growth (see, page 5878, column 1 fourth full paragraph and page 5879, column 2, first full paragraph, point (e)). Although the authors concluded that it was effective, there is no teaching or suggestion that any of these animals went into complete remission, or that the authors would expect to achieve complete remission in patients who were administered their immunotoxins.

The Examiner has pointed to no teaching or suggestion in the prior art that would lead one of skill to the conclusion that an immunotoxin comprising an REB4dsFv would have the degree of efficacy exhibited in Phase I clinical trials. As Applicants have explained in previous responses, RFB4dsFv-PE38 exhibited surprising clinical efficacy in Phase I clinical

trials for the treatment of hairy-cell leukemia. In Phase I trials, eleven of sixteen patients achieved complete remission and two parties achieved partial remission following treatment with RFB4ds(Fv)-PE38 (see, *New Engl. J. Med.* 345:241-247, 2001, which was previously supplied to the Examiner with Applicants' response filed May 10, 2007). The authors noted that they were unaware of any treatment that produced such a high rate of complete remission in hairy-cell leukemia that is resistant to purine analogues.

As further evidence that the degree of efficacy for the treatment of hairy cell leukemia is exceptional, provided herewith is a Declaration under 37 C.F.R. § 1.132 by Dr. Robert Kreitman. As can be seen from Dr. Kreitman's curriculum vitae, which is provided as an attachment to his Declaration, Dr. Kreitman holds the position of Chief of the Clinical Immunotherapy Section of the Laboratory of Molecular Biology in the Nation Cancer Institute. He has been a involved in over 20 clinical trials to investigate candidate therapeutic agents for the treatment of malignancies.

Dr. Kreitman explains that RFB4(dsFv)-PE38 was first assessed for toxicity and activity in 16 patients with purine-resistant hairy-cell leukemia in a Phase I dose-escalation trial. The results demonstrated a high response rate of the patients to this therapy. Of the 16 patients, 11 achieved complete remission and 2 achieved partial responses. The patients that achieved complete remission included three patients that had a variant of hairy-cell leukemia that responds poorly to any of the commonly used chemotherapeutic agents for hairy-cell leukemia. These results were striking enough to warrant publication in the *New England Journal of Medicine*. (Applicants note that the *New England Journal of Medicine* is a highly regarded journal that often has the highest impact factor of the journals of clinical medicine (see, *e.g.*, the accompanying page from a printout of a Wikipedia entry, which is attached hereto as Exhibit 1).

Dr. Kreitman further describes that a total of 31 patients with hairy-cell leukemia were evaluated in the phase I study. Of these patients, 19 (61%) had complete remission and 6 had partial remission. Dr. Kreitman compares this level of response to other hairy cell leukemia therapeutic agents. Rituximab, which a different cell surface antigen, has been tested in small trials of hairy-cell leukemia patients. In these tests, only 30% of 60 patients achieved a completed remission. Furthermore, Dr. Kreitman and his colleagues are unaware of any other

treatment, including interferon alpha, fludarabine, chlorambucil, and multiagent chemotherapy that can produce such a high rate of complete remission in purine analog-resistant hairy cell leukemia. Dr. Kreitman also compares the minimal residual disease in the 19 patients that had complete remission to the reported incidence (13% to 50%) of minimal residual disease observed in complete remission achieved using purine analogs. Of the 19 patients that achieved complete remission with BL22, only one patient had minimal residual disease as defined by the same criteria.

Dr. Kreitman concludes by unequivocally stating that although they had expected BL22 to exhibit a positive clinical effect for the treatment of hairy-cell leukemia, they were surprised at this unprecedented high level of response in these patients.

As evidenced by Dr. Kreitman's curriculum vitae, he is highly skilled in this art. The Examiner has provided no evidence or reasoning that Dr. Kreitman's conclusion (*i.e.*, that the clinical response achieved with BL22 was unexpected) is unfounded.

In view of the foregoing, the claims are patentable. Applicants therefore respectfully request withdrawal of the rejection.

### CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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